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Reaction of Isatins with 6-Amino Uracils and Isoxazoles: Isatin Ring-Opening vs. Annulations and Regioselective Synthesis of Isoxazole fused Quinoline Scaffolds in Water

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A green and efficient straightforward approach for the regioselective synthesis of novel isoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-diones and isoxazolo[5,4-b]quinolin-4-yl)-1H-pyrazol-5-amines *via* the cleavage of the isatin *C-N* bond followed by ring expansion reaction in one-pot manner has been established using environmentally benevolent *p*-toluene sulphonic acid as a catalyst. An exciting feature of this article is the reaction mechanism that depends on the nature of the group attached to the isatin ring nitrogen atom. The main advantages of this protocol include short reaction time, excellent yield, easy work-up, practical simplicity, high regioselectivity and the absence of extraction and chromatographic purification steps.

Introduction

One of the main challenges of heterocyclic-synthetic chemists is the development and implementation of efficient methodologies for the preparation of complex scaffolds and intermediates of biologically relevant compounds.[1] Multicomponent reactions (MCRs)[2] being efficient and effective methods in the sustainable and diversity oriented synthesis of heterocycles provide one of the most powerful platforms to access diversity as well as complexity from simple and inexpensive starting materials *via* generation of several bonds in a single synthetic operation, and are also of great relevance to green chemistry because of the diminished generation of the waste from organic solvents and chromatographic stationary phases associated with reduced number of intermediate purification steps.[3] Water is a non-flammable, non-hazardous, non-toxic, uniquely redox-stable, inexpensive solvent that has the additional advantage of being a non-exhaustible resource. Consequently, water is close to being an ideal green solvent, preferable to alternatives such as ionic liquids.[4] For these reasons, the development of synthetically useful reactions using water as the reaction medium has gained considerable interest.[5]

Among N-heterocyclic skeletons, fused quinolines have attracted the attention of chemists and biologists because they are key building blocks for the synthesis of biologically active natural products bearing quinoline skeletons.[6] In addition they are widely used in numerous commercial products, such as, pharmaceuticals, fragrances and dyes.[7] Molecules bearing quinoline skeletons have wide range of pharmaceutical activities, such as antitubercular,[8a] antimalarial,[8b] anti-inflammatory,[9] anticancer,[10] antibiotic,[11] antihypertensive,[12] platelet derived growth factor receptor tyrosine kinase (PDGF-RTK) inhibitory[13] and antihuman immunodeficiency virus (anti-HIV).[14] In particular, mefloquine (**1**) is still being used as an antimalarial, despite its side-effects (Figure 1).[15] Furthermore, a number of mefloquine analogues have been reported to possess antibacterial and antitubercular activities.[16] Synthetic quinoline **2**[(Mefloquine (2)] has antibacterial and antifungal activities.[17] From the point of view of synthetic chemistry, multicomponent one-pot reactions are known as an important strategy to extend the structural diversity of quinolines.[18] In this regard, the development of new multicomponent protocols for the synthesis of new quinoline-incorporating heterocycles has attracted considerable interest in recent years.[19]

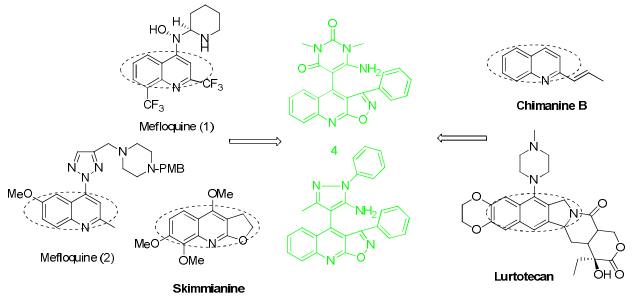


Figure 1 Design and synthesis of isoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-dione derivatives based on anti-TB and anti-cancer activity of Skimmianine, Mefloquine **1** and **2,** Lurtotecan and Chimanine B.

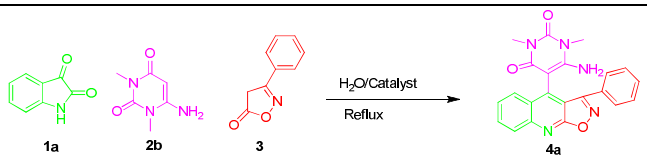
In addition isoxazoles represent an interesting class of heterocycles that display a range of biological properties, such as anti-inflammatory,[20] antimicrobial,[21] anticancer,[22] antinociceptive and anti-invasive.[23] A number of heterocyclic compounds fused with pyrimidines are known for their varied biological activities.[24] From a synthetic point of view, to date, methods for obtaining isoxazoloquinoline derivatives are still limited. Pardasani and co-workers[25] described a general photochemical synthesis of isoxazoloquinoline derivatives from isatin by 298-310 nanometer irradiations with long reaction times (48 hrs) and low yields (only 38 %) Thus, the pursuit of inexpensive and more environmentally benign methodologies for construction of fused quinolines motif still remains a challenge.

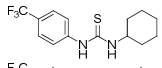
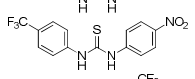
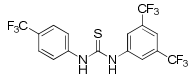
In view of the above, in the current paper, we report a novel one-pot multicomponent reaction for the construction of diverse isoxazoloquinolines and spiroxindoles based framework in water using a cheap catalyst, utilizing all the three reactants efficiently under thermal conditions with a high atom economy. To the best of our knowledge, three component reactions involving isatins, aminouracils and isoxazolones as coupling partners for the synthesis of isoxazoloquinoline and spiroxindole derivatives to date are not known. The present work forms a part of our ongoing research programme on the development of novel multicomponent reactions for the construction of important heterocyclic ring systems.[26]

Results and discussion

The considerations outlined above prompted us to investigate the multicomponent one-pot reactions of isatins, 6-amino uracils/amino pyrazole and isoxazolones, employing *P*-TSA.H_2O as a catalyst (Scheme 1), with a view to developing a highly convergent protocol for the synthesis of isoxazoloquinoline and spiroxindoles as attractive candidates for biological evaluation. While our planned reaction was unprecedented, there are two very recent literature reports describing the related multicomponent one-pot reacton of isatins, 6-amino uracils/amino pyrazole and isoxazolones. In one of these references, described a general two-component photochemical synthesis of isoxazoloquinoline derivatives[25] from isatin and isoxazolone by 298-310 nanometer irradiations using THF as a solvent, with long reaction times (48 hrs) and low yields (only 38 %) and spiroxindole derivatives from isatin and isoxazolone using ethanol as a solvent under thermal conditions with low yields (15 %). But in our case both the scaffolds (isoxazoloquinolines and spiroxindoles) obtained by three-component one-pot reaction of isatins, 6-aminouracils/amino pyrazole and isoxazolones under thermal conditions (Scheme 1) using water as a solvent with very good yields (up to 89 %) in short reaction times (3-5 h).

Table 1 Reaction optimization conditions:



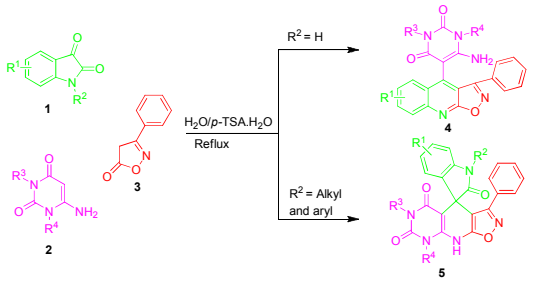
Entry	Catalyst (mol %)	Time (h)	Yield (%)					
			MeOH[a,b]	EtOH[a,b]	CH_3CN[a,b]	Neat[b]	IPA[a,b]	H_2O[a,b]
1.	$InCl_3$ (20 %)	10	15	Trace	Trace	20	Trace	15
2.	$SnCl_2.2H_2O$ (20%)	10	20	Trace	Trace	10	Trace	20
3.	*p*-TSA. H_2O (20 %)	7	60	30	20	20	15	89
4.	$BiCl_3$ (20 %)	12	Trace	10	Trace	Trace	Trace	25
5.	$AlCl_3$ (20 %)	10	20	30	10	30	Trace	25
6.	$FeCl_3$ (20 %)	15	Trace	30	Trace	12	20	30
7.	In $(OTf)_3$ (20 %)	17	20	25	20	Trace	Trace	35
8.	Cu $(OTf)_2$ (20 %)	12	15	Trace	10	15	Trace	25
9.	AgOTf (20 %)	10	10	15	Trace	10	Trace	35
10.	CF_3COOH	15	25	20	Trace	15	Trace	30
11.	L-Proline	18	15	Trace	Trace	20	Trace	15
12.		15	10	15	Trace	25	Trace	25
13.		15	20	25	Trace	15	Trace	20
14.		15	Trace	Trace	Trace	20	Trace	25
15.	*p*-TSA.H_2O (15 %)	7	50	25	Trace	20	Trace	55
16.	*p*-TSA.H_2O (10 %)	7	40	20	Trace	Trace	Trace	50
17.	*p*-TSA.H_2O (5 %)	7	40	Trace	Trace	15	Trace	50
18.	*p*-TSA.H_2O (25 %)	7	70	20	20	15	20	87
19.	*p*-TSA.H_2O (20 %)	4	74	40	15	20	15	89
20.	*p*-TSA.H_2O (20 %)	3	70	35	Trace	15	Trace	85
21.	*p*-TSA.H_2O (20 %)	2	50	15	Trace	15	Trace	70
22.	---------	20	<15	Trace	Trace	Trace	<10	<40
23.	*p*-TSA.H_2O (20 %/rt)	20	50	15	Trace	10	Trace	---

[a]The reaction was performed with isatin 1a (1 mmol), 6-amino uracil 2b (1 mmol), isoxazole 3 (1 mmol) and catalyst at reflux. [b] Isolated yields.

Whereas Bazgir *et al*.[27] described a general two-component synthesis of spiropyrimidine derivatives instead of spiroxindoles in different pathway from isatins and 6-aminouracils. Hence, one of our goals has been to synthesis both 6-amino uracil and isoxazole fused quinolines and spiroxindoles derivatives in one-pot.

To obtain the optimized conditions for the designed protocol based on the reaction of isatin (**1a**), 6-amino uracil (**2b**) and isoxazole **(3)** as model substrates, we checked different catalysts, solvents and temperatures and the results of this study are depicted in table 1.

We carried out the reaction using different Lewis acids (Table 1, entry 1, 2, 4, 5, 6, 7, 8, 9), Bronsted acid (Table 1, entry 10) and bifunctional organo catalysts (Table 1, entry 11, 12, 13, 14) to obtain the desired product (**4a**), with comparable results in all cases. Interestingly, when *P*-TSA.H_2O was used, the



Scheme 1 Synthesis of isoxazoloquinolines and spiroxindoles

reactivity was much improved. We also investigated the amount of *P*-TSA.H_2O required for this reaction and it was observed that with a decreasing amount of catalyst, the yields also decreased (Table 1, entry 15, 16, 17). Further increase of the catalyst loading from 20 to 25 mol % has no obvious influence on the reaction yield (Table 1, entry 18). Thus 20 mol % of *P*-TSA.H_2O in water is sufficient to enable the reaction in 4 h affording product **4a** in very good yield 89 % (Table 1, entry 19).

Subsequently, the effect of solvents was examined. Several organic solvents, such as EtOH, CH_3CN and IPA showed no superiority to MeOH. When the same reaction was performed in H_2O a good yield of product was observed after 4 h (Table 1, entry 19).

The scope of the reaction was further studied with various substituted isatin derivatives (Cl, Br, F, I, nitro, methyl) under the optimized reaction conditions, leading to the final products **4a-m** in very good yields (up to 89 %).

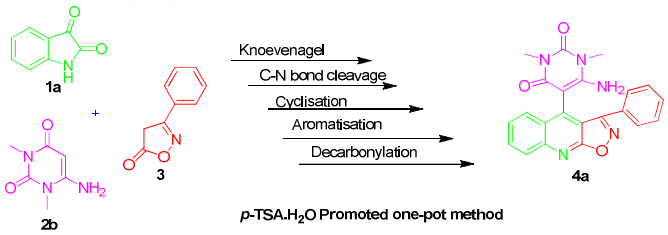
Next we sought to expand the substrate scope of the current method; N-substituted isatin (**1**) was examined (Scheme 5). Surprisingly, the desired isatin ring expansion derivatives were not obtained and the condensation products N-substituted spiro derivatives **5(a-h)** were obtained in good yields (Scheme 5) under the optimized conditions.

To extend our strategy further, we used amino pyrazole **6** instead of amino uracil **2** and isatin with various derivatives under similar conditions and the corresponding 3-methyl-1-phenyl-4-(3-phenylisoxazolo [5,4-b]-1H-pyrazol-5-amines **7(a-f)** were obtained in high yields (Scheme 5). We have shown that the use of a wide diversity of substituents in isatin **3** in this pseudo three component reaction makes possible the synthesis of libraries under similar circumstances (Scheme 5).

Accordingly, we have been able to prepare a library of isoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-diones **(4a-m),** isoxazolo[5,4-b]quinolin-4-yl)-1H-pyrazol-5-amines **(7a-f)** and spiroxindole derivatives **(5a-h)** (Scheme 5) using isatins, amino uracil and isoxazoles under green conditions. Consequently, after completion of the reactions, by simple filtration and washing with water and ethanol, the pure products can be obtained in good yield. This easy purification makes this methodology facile, practical and rapid to perform.

In recent years, it has become a popular notion that just because the reactions are conducted in sustainable media such as water or lower alcohols do not mean the method is "green" The environmental impact of a synthetic process is determined by factors such as the efficiency of the reaction, the workup process, and the clean-up or disposal of solvent. As per the synthetic protocol presented in this paper, the reactions were carried out in water using a cheap catalyst with good efficiency. The work-up process involves simple filtration and extraction and chromatography is not required. Furthermore, this reaction is a one-step process with a high atom economy and water is afforded as the by-product in this reaction. This approach therefore exemplifies the reconciliation of structural complexity and operational simplicity in an environmentally friendly time and cost effective manner. Significantly, the presence of amino groups at 5 and 6-positions on isoxazoloquinoline derivatives (Scheme 5, products **4a-m** and **7a-f**) makes these compounds excellent entrants as precursors for further synthetic renovations to meet the need for diverse useful purposes.

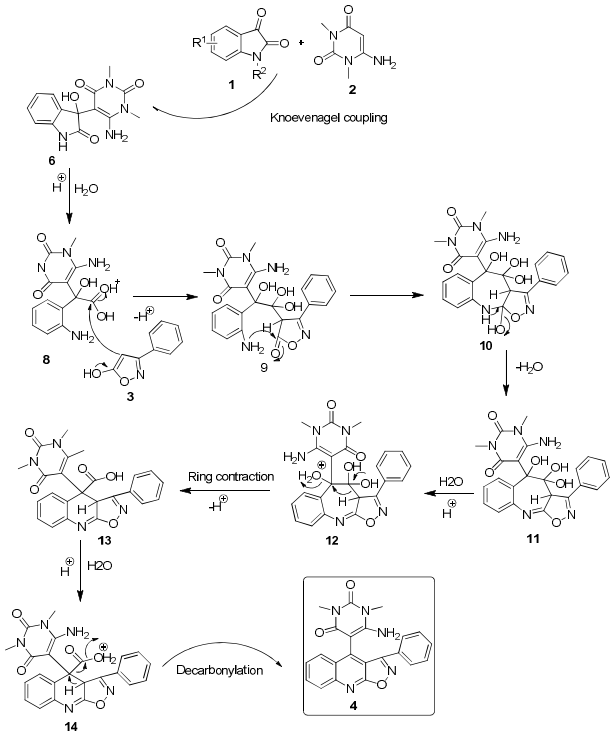
In this one-pot reaction, the course of the reaction was found to be dependent upon the nature of the group attached to the isatin ring nitrogen atom. When the nitrogen of isatin was not substituted, the polyfunctionalished heterocycles containing fused quinoline/isoxazole/uracil/pyrazole units were readily achieved *via* the cleavage of the isatin *C-N* bond followed by ring expansion to afford the desired quinoiline derivatives **4(a-m)** and **7(a-f),** In the case of N- alkyl/aryl/benzyl isatin, hydrolysis of isatin to isatic acid **(**Scheme 3**)** is sterically hindered by the N-substituent and as a result, the reaction is diverted to the other pathway, leading to the spiroxindole derivatives **5(a-h)** as outlined in scheme 5.



Scheme 2 Synthesis of isoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-dione (4)

By taking our entire experimental outcome into consideration, a tentative mechanistic interpretation for this new multicomponent reaction is outlined in scheme **3.** On the basis of the above mentioned results (Scheme 2), the knoevenagel condensation of isatin **1** with 6-aminouracil **2** affords intermediate 6.[27] In the presence of of *p*-TSA.H_2O, intermediate **6** can be converted to isatic acid **8**.[28] Simultaneously, *p*-TSA.H_2O as Bronsted acid assists the enolization of the isoxazole **3,** where isoxazole in the enol form then reacts with isatic acid **8** to form intermediate **9** followed by condensation *via* the elimination of water molecule, affording intermediate **11**, that could not be isolated. Acid catalysed ring contraction of this intermediate **11**, as visualised in the scheme would lead to the formation of **13** which can undergo acid catalysed decarbonylation to afford the final product **4**.

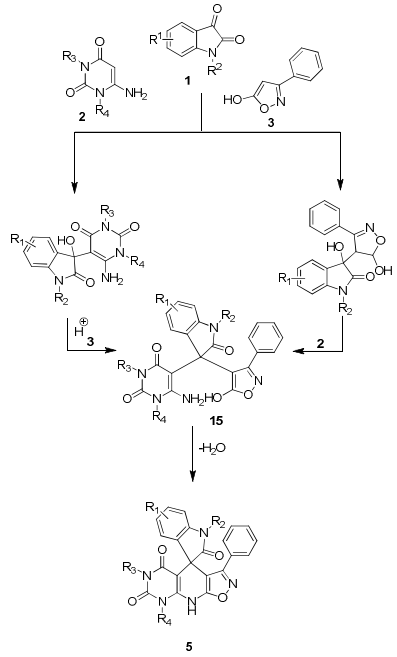
Decarboxylation of **13** followed by aromatisation by oxidation of the resulting dihydro intermediate would also lead to **14**. It turns out that the intermediates **11, 13** and **14** might be formed concomitantly



Scheme 3 Plausible mechanism for the formation of quinolines

and reacts instantly to limit the formation of by-products. Further investigation of the mechanism is to be conducted in due course.

We have not established the detailed mechanism for the formation of **5(a-h),** however a reasonable possibility is shown scheme 4. Apparently, the reaction proceeds through the intermediate **15** formed *in situ* by the reaction of the isatins **1**with 6-amino uracil **2** and isoxazole **3** followed by cyclisation affording the corresponding spiroxindoles **5(a-h)**.



Scheme 4 Plausible mechanism for the formation of spiroxindole **5(a-h)**

The structures of all the newly synthesized isoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-diones **4(a-m),** spiroxindoles **5(a-h)** and 3-methyl-1-phenyl-4-(3-phenylisoxazolo[5,4-b]-1H-pyrazol-5-amines **7(a-f)** are deduced by their satisfactory spectral (^{1}H NMR, ^{13}C NMR and EI-HRMS) studies. The structures of the two representative compounds **4d** and **5h** have been further confirmed by X-ray analysis [29, 30] (Figure 2 and 3)

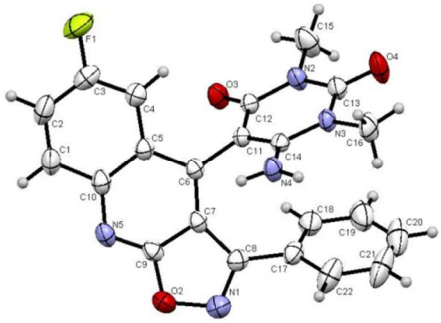


Figure 2 ORTEP diagram of compound **4d**

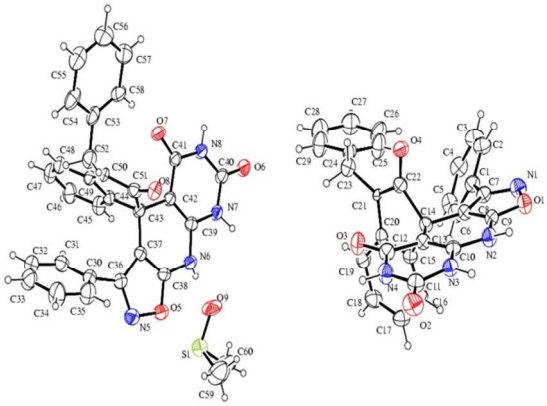
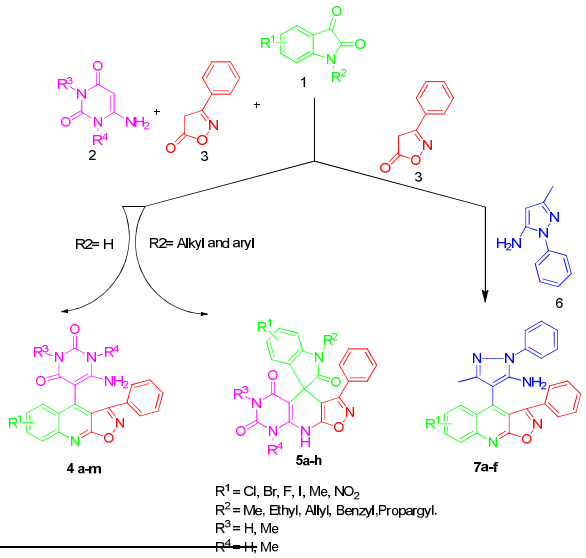
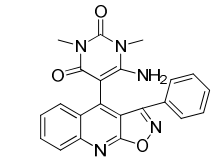
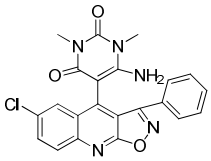


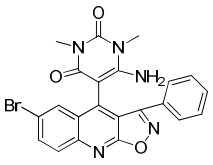
Figure 3 ORTEP diagram of compound **5h**

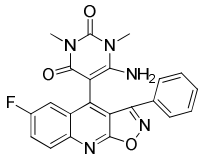
Scheme 5 Substrate scope for the synthesis of isoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-diones (**4a-m**)[a] , spiroxindole derivatives (**5a-h**)[a] and isoxazolo[5,4-b]quinolin-4-yl)-1H-pyrazol-5-amines (**7a-f**)[a]

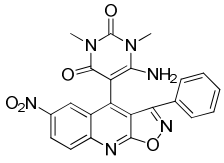


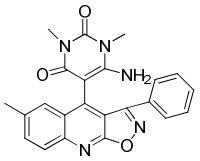

4a, 88 % Yield

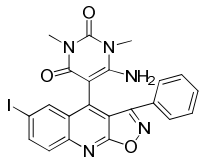

4b, 85 % Yield

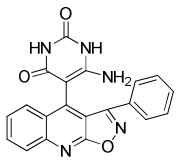

4c, 82 % Yield

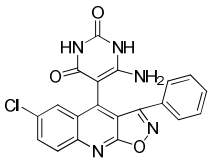

4d, 81 % Yield

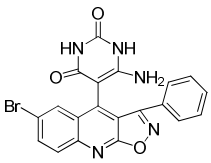

4e, 87 % Yield

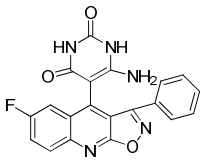

4f, 80 % Yield

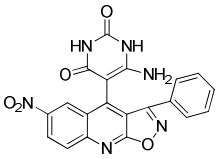

4g, 78 % Yield

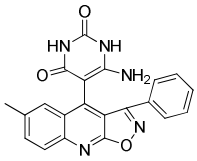

4h, 87 % Yield

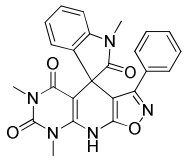

4i, 87 % Yield

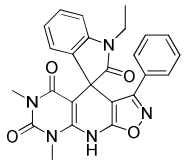

4j, 85 % Yield

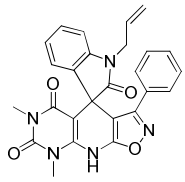

4k, 80 % Yield

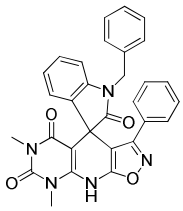

4l, 86 % Yield

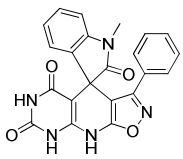

4m, 83 % Yield

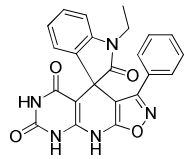

5a, 87 % Yield

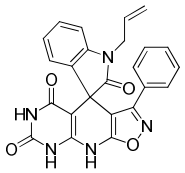

5b, 89 % Yield

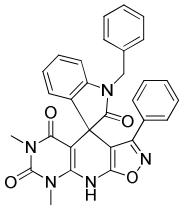

5c, 86 % Yield

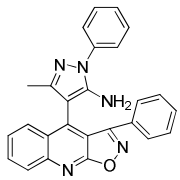

5d, 79 % Yield

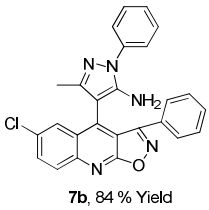

5e, 88 % Yield

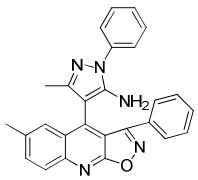

5f, 87 % Yield

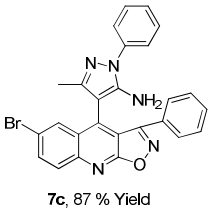

5g, 87 % Yield

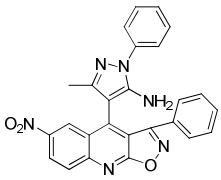

5h, 81 % Yield

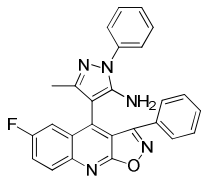

7a, 87 % Yield


7b, 84 % Yield


7f, 85 % Yield


7c, 87 % Yield


7d, 83 % Yield


7e, 77 % Yield

[a]The reaction was performed with isatin/N-substituted isatin **1** (1 mmol), 6-amino uracil **2**/6-amino pyrazole 6 (1 mmol), isoxazole **3** (1 mmol) and catalyst at reflux

Conclusion

In summary we have developed a novel and efficient one-pot multicomponent protocol for the synthesis of isoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-dione and isoxazolo[5,4-b]quinolin-4-yl)-1H-pyrazol-5-amines *via* the cleavage of the isatin *C-N* bond followed by ring expansion reaction and spiroxindole derivatives by cyclocondensation using environmentally benevolent *p*-toluene sulphonic acid monohydrate as the catalyst. In this one-pot reaction, the course of the reaction was found to be dependent upon the nature of the group attached to the isatin ring nitrogen atom, under the same conditions. Furthermore, the simple experimental procedure, utilization of an inexpensive, readily available and environmentally friendly catalyst and excellent yields are the advantages of the present methodology. These noteworthy advantages make the present methodology a very valuable addition to the existing methods available for the synthesis of isoxazolo quinoline and spiroxindole scaffolds. Further investigations are in progress in our laboratory to evaluate the process with a broader range of substrates to synthesize more complex products and evaluate their biological activities.

Experimental section:

All chemicals were purchased from Sigma Aldrich. Melting points are uncorrected. ^{1} H and ^{13} C NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard on a Bruker avance spectrometer at 400 Mhz amd 100 MHz respectively. Mass spectra were recorded using a JEOL GCMate-II – HR mass spectrometer. Analytical TLC was performed on precoated aluminium sheets of siliga gel G/UV-254 of 0.2 mm thickness (Merck, Germany).

General procedure for the preparation of quinoline and spiroxindole derivatives: A mixture of isatin/N-substituted isatin **1** (1 mmol), 6-amino uracil **2**/6-amino-1, 3-dimethyl uracil **2**/ amino pyrazol **6** (1 mmol), isoxazole 3 (1 mmol) and *p*-TSA.H_2O (0.20 mmol) in water (3 mL) were charged in a 25 mL round bottomed flask and the mixture was heated at reflux. The resulting solution was stirred for 3-5 h. The consumption of the starting material was monitored by TLC. The precipitated solid was filtred and washed with ethanol (5-7 mL), dried under vacuum to obtain pure **4a-m**, **5a-h** and **7a-f** in good yields (78-89 %). The identities of products **4a-m, 5a-h** and **7a-f** were confirmed by NMR and EI-HRMS, which are in good agreement with the assigned structures.

4a: 6-amino-1,3-dimethyl-5-(3-phenylisoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-dione

Isolated as white solid, 89 %, m.p: 263-265^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11. 50 (s, 1H), 10.86 (s, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.4 Hz, 2H), 7.22 (dd, J = 13.5, 6.1 Hz, 1H), 7.09 (d, J = 7.4 Hz, 2H), 7.03 – 6.96 (m, 2H), 6.88 (t, J = 7.5 Hz, 1H), 3.13 (s, 3H), 2.95 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.52, 163.15, 161.53, 157.22, 152.96, 151.14, 137.58, 129.80, 129.22, 129.14, 128.56, 128.43, 128.14, 127.72, 122.81, 120.01, 117.02, 95.20, 87.49, 51.59, 31.25, 27.51 ppm.

EI-HRMS: Anal. Calcd for C_{22} H_{17} N_5 O_3: 399.1331, Found: 399. 1323

4b: **6-amino-5-(6-chloro-3-phenylisoxazolo[5,4-b]quinolin-4-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione**

Isolated as white solid, 85 %, m.p: 260-262 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 11.04 (s, 1H), 7.43 (t, J = 7.3 Hz, 1H), 7.39 – 7.27 (m, 3H), 7.10 (dd, J = 12.4, 4.7 Hz, 3H), 7.03 (d, J = 8.7 Hz, 1H), 3.12 (s, 3H), 2.97 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.05, 162.90, 161.51, 157.28, 153.37, 151.16, 136.75, 129.85, 129.33, 128.90, 128.43, 128.15, 127.33, 126.54, 121.98, 118.62, 94.65, 87.53, 51.50, 31.27, 27.52 ppm.

EI-HRMS: Anal. Calcd for C_{22} H_{16} Cl N_5 O_3: 433.0942, Found: 433. 0942

4c: **6-amino-5-(6-bromo-3-phenylisoxazolo[5,4-b]quinolin-4-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione**

Isolated as white solid, 82 %, m.p: 275-278 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 11.14 (s, 1H), 7.49 (d, J = 24.2 Hz, 4H), 7.19 (t, J = 43.1 Hz, 4H), 3.21 (s, 3H), 3.07 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.06, 162.81, 161.52, 157.30, 153.38, 151.15, 137.17, 132.18, 130.06, 129.85, 128.89, 128.42, 128.15, 122.39, 119.02, 114.29, 94.67, 87.65, 51.44, 31.26, 27.53 ppm.

EI-HRMS: Anal. Calcd for C_{22} H_{16} Br N_5 O_3: 477. 0437, Found: 477. 0437

4d: **6-amino-5-(6-fluoro-3-phenylisoxazolo[5,4-b]quinolin-4-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione**

Isolated as white solid, 81 %, m.p: 258-260 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 10.90 (s, 1H), 7.43 (t, J = 7.3 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H), 7.16 – 7.06 (m, 3H), 7.06 – 6.99 (m, 1H), 6.96 (dt, J = 10.1, 5.1 Hz, 1H), 3.13 (s, 3H), 2.97 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.11, 163.27, 161.50, 157.25, 153.32, 151.18, 134.29, 129.83, 129.02, 128.42, 128.14, 121.66, 118.34, 116.53, 116.30, 114.19, 113.96, 94.59, 86.86, 51.72, 31.27, 27.51 ppm.

EI-HRMS: Anal. Calcd for C_{22} H_{16} F N_5 O_3: 417. 1237, Found: 417. 1270

4e: 6-amino-1,3-dimethyl-5-(6-nitro-3-phenylisoxazolo[5,4 b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-dione

Isolated as white solid, 87 %, m.p: 258-260 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 11.65 (s, 1H), 8.16 (dd, J = 9.0, 2.2 Hz, 1H), 7.84 (d, J = 2.2 Hz, 1H), 7.47 (t, J = 7.3 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.21 (d, J = 9.0 Hz, 1H), 7.10 (d, J = 7.6 Hz, 2H), 3.13 (s, 3H), 2.99 (d, J = 13.5 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.68, 162.20, 161.54, 157.38, 153.56, 151.10, 143.50, 142.59, 130.06, 128.56, 128.44, 128.19, 125.59, 124.13, 120.88, 117.49, 94.91, 88.90, 51.43, 31.38, 27.56 ppm.

EI-HRMS: Anal. Calcd for C_{22} H_{16} N_6 O_5: 444. 1182, Found: 444. 1134

4f: 6-amino-1,3-dimethyl-5-(6-methyl-3-phenylisoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-dione

Isolated as white solid, 80 %, m.p: 256-258 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (s, 1H), 10.72 (s, 1H), 7.43 (t, J = 7.3 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H), 7.06 (dd, J = 14.9, 7.9 Hz, 3H), 6.90 (d, J = 8.2 Hz, 1H), 6.79 (s, 1H), 3.13 (s, 3H), 2.96 (s, 3H), 2.14 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.60, 163.23, 161.52, 157.22, 152.92, 151.15, 135.25, 131.82, 129.90, 129.73, 129.23, 128.39, 128.14, 127.63, 119.81, 116.94, 95.11, 87.37, 51.58, 31.24, 27.51, 20.62 ppm.

EI-HRMS: Anal. Calcd for C_{23} H_{19} N_5 O_3: 413. 1488, Found: 413. 1486

4g: 6-amino-5-(6-iodo-3-phenylisoxazolo[5,4-b]quinolin-4-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione

Isolated as white solid, 78 %, m.p: 246-248 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1H), 11.00 (s, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.28 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 1H), 3.10 (s, 3H), 2.97 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.10, 162.68, 161.51, 157.30, 153.31, 151.13, 137.92, 137.63, 135.56, 129.82, 128.91, 128.41, 128.15, 122.65, 119.32, 94.75, 87.81, 85.71, 51.24, 31.26, 27.53 ppm.

EI-HRMS: Anal. Calcd for C_{22} H_{16} I N_5 O_3: 525. 0298, Found: 525. 0295

4h: 6-amino-5-(3-phenylisoxazolo [5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-dione
Isolated as white solid, 87 %, m.p: 268-270 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 10.40 (s, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.18 (dd, *J* = 7.9, 4.1 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 3.7 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 185.53, 168.02, 166.33, 163.76, 158.06, 156.08, 142.17, 134.74, 133.94, 133.46, 132.73, 131.99, 127.66, 125.01, 121.76, 99.82, 91.87, and 55.38 ppm.
EI-HRMS: Anal. Calcd for C_{20} H_{13} N_5 O_3: 371. 1013, Found: 371. 1012

4i: **6-amino-5-(6-chloro-3-phenylisoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-dione**
Isolated as white solid, 87 %, m.p: 280-282 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 10.44 (s, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.95 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.33, 163.01, 161.54, 159.08, 153.56, 151.21, 136.60, 130.06, 129.28, 128.93, 128.73, 127.98, 126.90, 126.51, 122.21, 118.62, 94.45, 87.14, 50.56 ppm.
EI-HRMS: Anal. Calcd for C_{20} H_{12} Cl N_5 O_3: 405. 0629, Found: 405. 0625

4j: 6-amino-5-(6-bromo-3-phenylisoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-dione
Isolated as white solid, 85 %, m.p: > 350 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 1H), 11.69 (s, 1H), 10.90 (d, J = 168.6 Hz, 1H), 10.07 (s, 1H), 7.84 – 7.55 (m, 2H), 7.23 (dd, J = 95.7, 31.5, 20.1, 7.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.03, 162.63, 160.49, 153.99, 149.64, 141.56, 139.66, 138.49, 133.97, 133.86, 129.27, 129.19, 128.92, 127.76, 122.87, 114.46, 112.10, 103.17, 90.46, 62.61 ppm.
EI-HRMS: Anal. Calcd for C_{20} H_{12} Br N_5 O_3: 449. 0124, Found: 449. 0123

4k: 6-amino-5-(6-fluoro-3-phenylisoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-dione
Isolated as white solid, 80 %, m.p: 286-288 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 11.03 (s, 1H), 10.87 (s, 1H), 10.45 (s, 1H), 7.47 (t, J = 7.3 Hz, 1H), 7.38 (t, J = 7.4 Hz, 2H), 7.13 (dd, J = 14.6, 8.0 Hz, 3H), 7.02 (dd, J = 8.6, 5.1 Hz, 1H), 6.85 (d, J = 9.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.36, 163.36, 161.52, 159.06, 157.08, 153.52, 151.21, 134.13, 130.01, 129.04, 128.69, 127.97, 121.90, 118.23, 116.48, 116.25, 113.83, 113.60, 94.31, 86.52, 50.76 ppm.
EI-HRMS: Anal. Calcd for C_{20} H_{12} F N_5 O_3: 389. 0924, Found: 389. 0928

4l: 6-amino-5-(6-nitro-3-phenylisoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-dione
Isolated as white solid, 86 %, m.p: 294-296 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 11.82 (s, 1H), 11.29 (s, 1H), 10.59 (s, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.70 (s, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.42 (t, J = 7.3 Hz, 2H), 7.23 – 7.12 (m, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.00, 162.36, 161.58, 159.05, 153.62, 151.14, 143.27, 142.49, 130.30, 128.88, 128.49, 127.99, 125.51, 123.47, 121.07, 117.46, 94.95, 88.36, 50.46 ppm.
EI-HRMS: Anal. Calcd for C_{20} H_{12} N_6 O_5: 416. 0869, Found: 416. 0865

4m: 6-amino-5-(6-methyl-3-phenylisoxazolo[5,4-b]quinolin-4-yl)pyrimidine-2,4(1H,3H)-dione
Isolated as white solid, 83 %, m.p: 262-264 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 – 10.43 (s, 4H), 7.46 (t, J = 7.4 Hz, 2H), 7.38 (t, J = 7.4 Hz, 4H), 7.15 (d, J = 5.3 Hz, 4H), 7.03 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 8.1 Hz, 2H), 6.69 (s, 2H), 2.16 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.88, 163.33, 161.57, 159.01, 153.23, 151.33, 135.07, 131.83, 129.93, 129.85, 129.25, 128.68, 127.97, 127.16, 120.07, 116.94, 94.99, 86.96, 50.57, 20.65 ppm.
EI-HRMS: Anal. Calcd for C_{21} H_{15} N_5 O_3: 385. 1175, Found: 385. 3647

5a: 1,6',8'-trimethyl-3'-phenyl-5'H-spiro[indoline-3,4'-isoxazolo[4',5':5,6]pyrido[2,3-d]pyrimidine]-2,5',7'(6'H,8'H,9'H)-trione
Isolated as white solid, 87 %, m.p: 250-252 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 7.47 (dd, J = 24.0, 6.8 Hz, 2H), 7.34 – 7.10 (m, 4H), 7.02 (dt, J = 14.7, 7.3 Hz, 1H), 6.69 (t, J = 7.4 Hz, 2H), 3.60 (s, 3H), 3.14 (d, J = 53.9 Hz, 3H), 2.89 (d, J = 104.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.28, 177.06, 161.50, 161.03, 160.20, 150.71, 146.74, 143.50, 135.57, 129.93, 128.39, 128.37, 128.15, 127.78, 123.85, 122.72, 108.13, 93.96, 88.58, 51.28, 40.37, 40.16, 39.95, 39.74, 39.53, 31.30, 28.06, 26.14 ppm.
EI-HRMS: Anal. Calcd for C_{24} H_{19} N_5 O_4: 441. 1437, Found: 441.1435

5b: 1-ethyl-6',8'-dimethyl-3'-phenyl-5'H-spiro[indoline-3,4'isoxazolo[4',5':5,6]pyrido[2,3-d]pyrimidine]-2,5',7'(6'H,8'H,9'H)-trione
Isolated as white solid, 89 %, m.p: 256-258 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (s, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.19 (dt, *J* = 14.9, 7.5 Hz, 4H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.55 (d, *J* = 7.5 Hz, 2H), 3.53 (s, 3H), 3.20 (dd, *J* = 15.5, 8.6 Hz, 2H), 3.00 (s, 3H), 0.69 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.57, 161.49, 161.19, 160.17, 150.70, 146.59, 143.16, 136.00, 129.98, 128.84, 128.50, 128.47, 127.99, 124.16, 122.57, 108.40, 93.68, 88.82, 48.41, 34.50, 31.28, 28.09, 12.02 ppm.
EI-HRMS: Anal. Calcd for C_{25} H_{21} N_5 O_4: 455. 1594, Found: 455.1425

5c: 1-allyl-6',8'-dimethyl-3'-phenyl-5'H-spiro[indoline-3,4'-isoxazolo[4',5':5,6]pyrido[2,3-d]pyrimidine]-2,5',7'(6'H,8'H,9'H)-trione
Isolated as white solid, 86 %, m.p: 252-254 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.24 – 7.12 (m, 4H), 6.96 (t, J = 7.4 Hz, 1H), 6.56 (t, J = 8.0 Hz, 3H), 5.32 (d, J = 3.5 Hz, 2H), 5.04 – 4.94 (m, 1H), 4.02 (d, J = 16.5 Hz, 1H), 3.54 (s, 3H), 3.50 (d, J = 2.8 Hz, 1H), 3.01 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.80, 161.49, 161.08, 160.20, 150.70, 146.76, 142.90, 135.77, 132.05, 129.97, 128.65, 128.51, 128.45, 127.83, 124.00, 122.77, 117.57, 108.93, 93.80, 88.56, 49.08, 48.46, 42.36, 31.32, 28.12 ppm.
EI-HRMS: Anal. Calcd for C_{26} H_{21} N_5 O_4: 467. 1594, Found: 467. 1534

5d: 1-benzyl-6',8'-dimethyl-3'-phenyl-5'H-spiro[indoline 3,4'isoxazolo[4',5':5,6]pyrido[2,3-d]pyrimidine]-2,5',7'(6'H,8'H,9'H)-trione
Isolated as white solid, 79 %, m.p: 265-267 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.33 – 7.17 (m, 8H), 7.08 (t, J = 7.7 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.63 (d, J = 7.7 Hz, 2H), 6.33 (d, J = 7.8 Hz, 1H), 4.78 (d, J = 16.3 Hz, 1H), 3.94 (d, J = 16.3 Hz, 1H), 3.56 (s, 3H), 3.07 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.50, 161.53, 161.04, 160.28, 159.77, 150.71, 146.80, 142.93, 136.32, 135.77, 130.11, 128.77, 128.65, 128.54, 128.43, 127.82, 127.77, 127.47, 127.42, 124.08, 122.93, 108.97, 93.84, 88.58, 48.65, 43.96, 31.35, 28.15 ppm.
EI-HRMS: Anal. Calcd for C_{30} H_{23} N_5 O_4: 517. 1750, Found: 517. 1745

5e: 1-methyl-3'-phenyl-5'H-spiro[indoline-3,4'-isoxazolo[4',5':5,6]pyrido[2,3-d]pyrimidine]-2,5',7'(6'H,8'H,9'H)-trione

Isolated as white solid, 88 %, m.p: 308-310 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 2H), 10.86 (s, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.25 – 7.13 (m, 3H), 7.09 (d, J = 7.2 Hz, 1H), 6.93 (t, J = 7.4 Hz, 1H), 6.61 (d, J = 7.0 Hz, 3H), 2.68 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.87, 163.34, 161.58, 159.02, 153.30, 151.39, 135.08, 131.84, 129.93, 129.85, 129.26, 128.68, 127.98, 127.16, 120.09, 116.95, 95.01, 86.98, 50.58, 20.65 ppm.
EI-HRMS: Anal. Calcd for C_{22} H_{15} N_5 O_4: 413. 1124, Found: 413. 1122

5f: 1-ethyl-3'-phenyl-5'H-spiro[indoline-3,4' isoxazolo[4',5':5,6]pyrido[2,3-d]pyrimidine]-2,5',7'(6'H,8'H,9'H)-trione
Isolated as white solid, 87 %, m.p: 298-300 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 2H), 10.83 (s, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.25 – 7.10 (m, 4H), 6.97 (t, J = 7.4 Hz, 1H), 6.70 (d, J = 7.7 Hz, 1H), 6.56 (d, J = 7.5 Hz, 2H), 3.18 (dd, J = 13.0, 8.0 Hz, 2H), 0.72 (t, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.52, 162.11, 161.58, 161.02, 150.45, 146.38, 143.15, 135.71, 129.94, 128.82, 128.44, 128.02, 124.10, 122.60, 108.40, 93.61, 88.57, 47.55, 34.45, 11.92 ppm.
EI-HRMS: Anal. Calcd for C_{23} H_{17} N_5 O_4: 427. 1281, Found: 427. 1285

5g: 1-allyl-3'-phenyl-5'H-spiro[indoline-3,4'-isoxazolo[4',5':5,6]pyrido[2,3-d]pyrimidine]-2,5',7'(6'H,8'H,9'H)-trione Isolated as white solid, 87 %, m.p: 300-302 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 2H), 10.89 (s, 1H), 7.35 (t, J = 7.3 Hz, 1H), 7.24 – 7.11 (m, 4H), 6.96 (t, J = 7.3 Hz, 1H), 6.54 (dd, J = 20.9, 7.5 Hz, 3H), 5.50 – 5.26 (m, 2H), 4.97 (d, J = 10.1 Hz, 1H), 4.05 (d, J = 16.1 Hz, 1H), 3.48 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.81, 162.20, 161.59, 160.89, 150.44, 146.62, 142.88, 135.46, 131.87, 129.92, 128.63, 128.46, 128.40, 127.86, 123.92, 122.81, 117.20, 108.94, 93.79, 88.24, 74.60, 47.61, 42.22 ppm.
EI-HRMS: Anal. Calcd for C_{24} H_{17} N_5 O_4: 439. 1281, Found: 439. 1280

5h: 1-benzyl-6',8'-dimethyl-3'-phenyl-5'H-spiro[indoline-3,4'-isoxazolo[4',5':5,6]pyrido[2,3-d]pyrimidine]-2,5',7'(6'H,8'H,9'H)-trione
Isolated as white solid, 81 %, m.p: 254-256 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (s, 2H), 11.05 (s, 1H), 7.49 (t, J = 7.4 Hz, 1H), 7.44 – 7.21 (m, 8H), 7.15 (dd, J = 16.0, 7.8 Hz, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.70 (d, J = 7.4 Hz, 2H), 6.34 (d, J = 7.7 Hz, 1H), 4.95 – 4.84 (m, 1H), 3.93 (d, J = 16.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.36, 162.44, 161.81, 161.60, 160.86, 150.38, 149.91, 146.79, 144.45, 142.78, 136.29, 135.47, 130.03, 128.74, 128.62, 128.50, 128.39, 127.82, 127.55, 127.42, 127.32, 124.02, 122.98, 108.97, 93.89, 88.09, 47.78, 43.79 ppm.
EI-HRMS: Anal. Calcd for C_{28} H_{19} N_5 O_4: 489. 1437, Found: 489. 1435

7a: 3-methyl-1-phenyl-4-(3-phenylisoxazolo[5,4-b]quinolin-4-yl)-1H-pyrazol-5-amine
Isolated as white solid, 87 %, m.p: 255-257 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 1H), 10.54 (s, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.58 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.20 (dd, J = 13.9, 7.0 Hz, 3H), 7.11 (d, J = 7.3 Hz, 1H), 6.97 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 7.5 Hz, 2H), 6.74 (d, J = 7.7 Hz, 1H), 1.54 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.40, 165.11, 161.94, 145.61, 141.76, 139.44, 138.36, 135.08, 129.98, 129.94, 129.38, 128.70, 128.55, 128.30, 127.66, 125.30, 123.34, 123.03, 110.05, 101.27, 92.94, 47.49, 11.82 ppm.
EI-HRMS: Anal. Calcd for C_{26} H_{19} N_5 O: 417. 1590, Found: 417. 1544

7b: 4-(6-chloro-3-phenylisoxazolo[5,4-b]quinolin-4-yl)-3-methyl-1-phenyl-1H-pyrazol-5-amine
Isolated as white solid, 84 %, m.p: 220-222 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 10.65 (s, 1H), 7.68 – 7.54 (m, 4H), 7.44 (t, J = 7.0 Hz, 1H), 7.37 (d, J = 7.3 Hz, 1H), 7.27 – 7.18 (m, 4H), 6.90 (d, J = 7.5 Hz, 2H), 6.71 (d, J = 8.0 Hz, 1H), 1.55 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.21, 165.08, 161.79, 145.39, 140.56, 139.59, 138.29, 136.88, 130.02, 129.96, 129.28, 128.64, 128.57, 128.24, 127.75, 126.99, 125.47, 123.51, 111.48, 100.56, 92.39, 56.52, 19.01 ppm,
EI-HRMS: Anal. Calcd for C_{26} H_{18} Cl N_5 O: 451. 1200, Found: 451. 1234

7c: 4-(6-bromo-3-phenylisoxazolo[5,4-b]quinolin-4-yl)-3-methyl-1-phenyl-1H-pyrazol-5-amine
Isolated as white solid, 87 %, m.p: 230-232 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.26 (s, 1H), 10.68 (s, 1H), 7.68 – 7.56 (m, 4H), 7.49 – 7.31 (m, 4H), 7.24 (t, J = 6.9 Hz, 2H), 6.91 (d, J = 7.1 Hz, 2H), 6.68 (d, J = 7.9 Hz, 1H), 1.57 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.08, 165.09, 161.80, 145.41, 140.95, 139.59, 138.28, 137.27, 132.15, 130.89, 130.04, 129.95, 129.77, 128.65, 128.57, 128.24, 127.76, 124.36, 123.52, 114.62, 112.01, 100.55, 92.40, 56.54, 19.01 ppm.
EI-HRMS: Anal. Calcd for C_{26} H_{18} Br N_5 O: 495. 0695, Found: 495. 0654

7d: 3-methyl-4-(6-nitro-3-phenylisoxazolo[5,4-b]quinolin-4-yl)-1-phenyl-1H-pyrazol-5-amine
Isolated as white solid, 83 %, m.p: 216-218 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.33 (s, 1H), 11.19 (s, 1H), 7.62 (dd, J = 18.7, 7.0 Hz, 4H), 7.47 (t, J = 7.2 Hz, 2H), 7.35 (d, J = 6.9 Hz, 1H), 7.22 (d, J = 6.7 Hz, 2H), 7.12 (d, J = 7.1 Hz, 1H), 6.86 (d, J = 5.7 Hz, 3H), 1.53 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.94, 165.08, 161.79, 147.88, 145.28, 143.40, 139.86, 138.21, 135.64, 129.97, 128.70, 128.53, 128.28, 126.56, 125.97, 123.69, 121.13, 110.28, 101.00, 99.78, 93.82, 92.09, 47.43, 21.25 ppm.
EI-HRMS: Anal. Calcd for C_{26} H_{18} Br N_6 O_3: 462. 1440, Found: 462. 1432

7e: 4-(6-fluoro-3-phenylisoxazolo[5,4-b]quinolin-4-yl)-3-methyl-1-phenyl-1H-pyrazol-5-amine
Isolated as white solid, 77 %, m.p: 234-236 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.23 (s, 1H), 10.57 (s, 1H), 7.67 – 7.54 (m, 4H), 7.44 (t, *J* = 7.1 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.03 (dd, *J* = 20.8, 8.9 Hz, 2H), 6.91 (d, *J* = 7.5 Hz, 2H), 6.70 (dd, *J* = 8.1, 3.9 Hz, 1H), 1.55 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.50, 165.07, 161.85, 160.24, 157.87, 145.48, 139.53, 138.29, 137.89, 136.51, 129.99, 128.61, 128.58, 128.25, 127.74, 123.44, 115.90, 115.67, 113.15, 112.91, 110.86, 100.70, 92.49, 47.97, 11.81 ppm.
EI-HRMS: Anal. Calcd for C_{26} H_{18} F N_5 O: 435. 1495, Found: 435. 1492

7f: 3-methyl-4-(6-methyl-3-phenylisoxazolo[5,4-b]quinolin-4-yl)-1-phenyl-1H-pyrazol-5-amine
White solid, 85 %, m.p: 235-237 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 10.41 (s, 1H), 7.67 – 7.54 (m, 4H), 7.43 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.19 (t, J = 7.6 Hz, 2H), 7.02 (d, J = 7.8 Hz, 1H), 6.94 (s, 1H), 6.85 (d, J = 7.4 Hz, 2H), 6.63 (d, J = 7.8 Hz, 1H), 2.21 (s, 3H), 1.54 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.29, 165.07, 161.89, 145.61, 139.36, 139.29, 138.36, 135.29, 132.04, 129.98, 129.63, 128.73, 128.56, 128.31, 127.63, 125.74, 123.31, 109.80, 101.43, 93.00, 47.50, 21.03, 11.84 ppm.
EI-HRMS: Anal. Calcd for C_{27} H_{21} N_5 O: 431. 1746, Found: 431. 1734

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29 Crystal data for product 4d (CCDC-:1020838, Figure 1): C_{22} H_{16} F N_5 O_3, crystallised in the monoclinic, space group P 2(1)/c with the following unit cell parameters a = 13.3119(5) A alpha = 90 deg., b = 10.7033(4) A beta = 91.8261(12) deg., c = 13.8141(4) A gamma = 90 deg:

30 Crystallographic data for compound **5h** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC- 10355. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 762911 ore-mail: deposit@ccdc.cam.ac.uk].